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Pipeline

Expedited regulatory product approval in the time of COVID-19

The COVID-19 pandemic has given us a new appreciation for the need for scientifically-driven research and development. The availability of vaccines within a relatively short period after the onset of the pandemic is a wonder from my perspective. Hand-in-hand with the science was a flexible regulatory environment, making vaccines available initially through an Emergency Use Authorization (EUA) from the U.S. Food and Drug Administration, and then full approval. This leads to another question – are there other life-saving and sight-saving treatments which should enjoy a similarly faster regulatory pathway to treating patients?

The short answer is that the U.S. there IS a pathway – actually several pathways. I wrote about this issue, and how it might apply to ophthalmic drugs about ten years ago [1]. Briefly, the key U.S. law governing drug approval is the 1962 Kefauver-Harris amendment which requires “substantive evidence of safety and efficacy” of a new pharmaceutical in well controlled studies. A subsequent law was the Orphan Drug Act of 1983 which provided financial incentives and consulting support for development of drugs to treat rare diseases (defined as less than 200,000 affected Americans) [2]. In 1992, the FDA issued regulations for Accelerated Approval, allowing earlier approval of drugs to treat serious diseases. In 2012, Congress passed the Food and Drug Administration Safety Innovation Act, which amended the Federal Food, Drug, and Cosmetic Act, to allow FDA to base accelerated approval on whether the drug has an effect on a surrogate or an intermediate clinical endpoint. This regulation, called “Subpart H”, allows for an accelerated conditional approval of a drug based upon a surrogate basis (21 CFR 314.510). The Sponsor is obligated to conduct post-approval studies with the drug using the “real” endpoint. There have been nearly 300 drugs approved using this pathway. For the most part, they are drugs for treatment of cancer and of pain [2]. If subsequent studies with the “real” measure do NOT show a favorable benefit-risk, then the approval will be withdrawn. This has occurred, perhaps most notably with the removal of bevacizumab’s conditional approval for the treatment of breast cancer [3]. As I review the list of approvals via this route, I do not see any drugs for the treatment of ocular disease, much less treatment of ocular surface disease. Decades before this law was enacted, the U.S. FDA and many other regulatory authorities approved treatments for glaucoma based on the lowering of intraocular pressure (IOP). Technically, these approvals are NOT Subpart H, and there is no obligation for follow-on studies on prevention of visual field progression. They are based upon the world-wide agreement that elevated IOP is a major risk factor for glaucoma.

The U.S. FDA Center for Drug Evaluation and Research has four key expedited programs for serious conditions for drugs and biologics - Fast Track, Breakthrough Therapy, Accelerated Approval and Priority Review. The qualifications and the benefits of each program are presented in an FDA guidance [4]. In my experience, “Breakthrough Therapy” designation is the most valuable. However, it requires clinical evidence

of efficacy, typically from pilot trials with concurrent controls. Other centers at FDA also have similar programs. The Center for Biologics Evaluation and Research has “Regenerative Medicine Advanced Therapy Designation”, which was part of the 21st Century Cures Act of 2016 [5]. The Center for Devices and Radiological Health has the “Breakthrough Devices Program” [6].

In June 2021, Biogen received approval for a Biologic License Application for its aducanumab-avwa (Aduhelm™) for the treatment of Alzheimer’s disease. The basis for this approval was the reduction of amyloid beta plaque (as evaluated using positron emission tomography in three controlled trials). This FDA approval was in contrast to the negative vote of an external, non-binding, advisory panel in November 2020. In this “accelerated approval”, FDA cited 21 CFR 601.41, requiring a post-approval study by the Sponsor “... in order to verify the clinical benefit of aducanumab, conduct a randomized, controlled trial to evaluate the efficacy of aducanumab-avwa compared to an appropriate control for the treatment of Alzheimer’s disease. The trial should be of sufficient duration to observe changes on an acceptable endpoint in the patient population enrolled in the trial” with a due date for a protocol of October 2021, and completion and reporting of that long-term trial by 2030.

Subsequently, the editors of *JAMA Internal Medicine* published three perspectives on this approval [7]. Senior management at FDA presented the basis of their approval in peer-reviewed journals, frankly stating that there were some discrepant results in the studies. They also noted the safety risks. In the end, in considering the benefits and risk of this treatment, FDA considered the degenerative nature of Alzheimer’s disease, and testimonials from patients and their families. FDA conditionally approved the treatment using the accelerated pathway, with the previous statement post-approval requirement for additional studies [8]. The second perspective was from Crosson (affiliated with a Health Management Organization) who noted the possibilities for harm from the medication and that “the cost of this drug alone might threaten the financial viability of the program,” they argue that the Centers for Medicare & Medicaid Services “should use independent clinical and pharmacologic experts to evaluate the strength of the evidence for the efficacy and safety of aducanumab and arrive at its own findings.” [9] The third perspective from academicians Gyawali et al. drew on the experience with accelerated approvals with oncology drugs, call for reforming the FDA’s accelerated approval pathway. Among Gyawali et al.’s recommendations were timely completion of postapproval trials, the verification of clinical benefit with clinical end points, and the “prompt and automatic” withdrawal of an indication for a drug granted under accelerated approval if the confirmatory trial is negative [9].

Neurology also published perspectives on this topic [10]. Salloway and Cummings present the clinical trial reports showing consistent reduction of β -amyloid (A β) on amyloid PET [11]. In a

counterviewpoint, Knopman and Perlmutter argue that the clinical benefit of aducanumab seen was small, amounting to 3 months' worth of delay in clinical decline [12]. *New England Journal of Medicine* also had articles on this topic [13,14]. Commentaries in the medical literature continue, including cost-effectiveness calculations and public policy discussions [15–17].

With hundreds of accelerated approvals over the years, why has the approval of aducanumab been so controversial? Is it because of the indication (Alzheimer's disease), the validity of the biomarker, A β , to predict disease progression, the weight of the efficacy evidence, or the safety concerns? I think it is all of those – but primarily it is the cost. The initial “wholesale average cost” was initially estimated at approximately \$56,000 per patient per year [18], and more recently as \$28,200 (March 2022) [19]. The ocular gene therapy Luxturna® (voretigene neparvovec-rzyl) is at least ten times this cost – but as a gene therapy, it is thought to be longer acting. As well, the U.S. patient population with the label “confirmed biallelic RPE65 mutation-associated retinal dystrophy” is 3000 or less [20] – many orders of magnitude less than the U.S. population with, or at risk for Alzheimer's disease. Thus the estimates for the impact of this cost per patient times the number of patients has many concerned about the impact on federal and state budgets [21,22]. In late 2021, Medicare announced increased insurance premiums for beneficiaries for 2022, with some claiming it is due to the anticipated costs of including aducanumab on the formulary. However, subsequently, the magnitude of this increase was announced – it is approximately \$1 per month – which I consider negligible. In February 2022, the U.S. Centers for Medicare and Medicaid Services proposed last month to limit coverage of Biogen's drug Aduhelm® (aducanumab-avwa) to patients enrolled in clinical trials sanctioned by the agency. These announcements are now moot, given that in early May 2022, the company announced they would not be selling the product in the U.S. at this time. However, Medicare's “coverage with evidence of development” [23] may have impact on future accelerated approvals.

In my opinion, the carrot-and-stick accelerated approval – wherein there is the potential for making novel therapies available earlier for patients with blinding or sight-threatening disease, but with the condition that the approval may be removed if this is not borne out in longer-term “real” studies – is a good balance of benefit/risk. Stated differently, if this pathway (and the other expedited programs) did not exist, many patients and health care providers would advocate for its creation. I believe that the accelerated programs used by FDA to meet the COVID-19 pandemic have proven to be worth the risk. A critical review of the early approval pathways in the U.S. and Europe has been recently published [24].

In a potentially similar situation, Amylyx has a New Drug Application pending with the U.S. FDA for its AMX0035 (sodium phenylbutyrate and taurisodiol) for the treatment of amyotrophic lateral sclerosis. In a meeting in March, a non-binding advisory panel voted in favor of efficacy, based upon a single Phase 2 study. It will be interesting to see FDA's decision (due in June 2022), and the healthcare system response.

In ophthalmology, and ocular surface disease specifically, unfortunately, other than IOP for glaucoma, there is no validated biomarker [25]. Thus to date, the accelerated approval has not been used in our field. The optimist in me feels that our continued research will find better biomarkers, as well as finding novel treatments, some of which might one day be suitable for an accelerated approval.

Declaration of Competing Interest

Gary D. Novack PhD consults with numerous pharmaceutical and medical device firms.

Appendix

News from pharmaceutical and medical device companies.

Ophthalmic products related to the ocular surface

- Aldeyra Therapeutics announced completion of enrollment in its phase 3 TRANQUILITY-2 trial of 0.25% reproxalap ophthalmic solution in patients with dry eye disease (April 2022).
- Bausch + Lomb and Novaliq presented results from its first pivotal phase 3 trial (GOBI) of NOV03 (perfluorohexyloctane) in patients with dry eye disease (DED, April 2022).
- Mylan received U.S. FDA approval for its generic form of Restasis® (cyclosporine ophthalmic emulsion (February 2022).
- Nicox's NCX 4251 (fluticasone), previously being evaluated for treatment of non-infectious blepharitis, will now be evaluated for the treatment of dry eye disease (February 2022).
- TearSolutions is planning Phase 3 studies of its Lacriprep for the treatment of dry eye disease (February 2022).
- VivaVision Biotech announced topline results from a Phase 2 clinical study of VVN001 in patients with dry eye disease (March 2022).

Ophthalmic products not related to the ocular surface

- Allergan announced that the phase 3 VIRGO trial evaluating the safety and efficacy of investigational twice-daily administration of Vuity® (pilocarpine HCl ophthalmic solution) 1.25% in adults with presbyopia met its primary efficacy endpoint (April 2022).
- Apellis announced 18 month data on its pegcetacoplan in patients with geographic atrophy (GA) from its DERBY and OAKS Studies (March 2022).
- Bausch + Lomb launched an initial public offering (IPO, April 2022).
- Belite Bio launched an IPO to develop its LBS-008 for the treatment of retinal degenerative eye disease (April 2022).
- Biogen announced it will withdraw a marketing application of its Aduhelm® (aducanumab-avwa) in Europe, and marketing in the U.S. (May 2022).
- EyeBio is developing a diversified pipeline of ophthalmic product candidates that combines scientifically compelling targets with innovative translational approaches (February 2022).
- Eyepoint announced results from its ongoing Phase 1 study of its EYP-1901 (vorolanib) for the treatment of wet age-related macular degeneration (wet age-related macular degeneration (AMD), February 2022).
- Fera Pharmaceuticals announced a long-term manufacturing agreement for Phospholine Iodide® (echothiophate iodide) with a U.S. based contract manufacturer (February 2022).
- Genentech received U.S. FDA approval for its Vabysmo™ (faricimab-svoa), an intravitreal bispecific antibody for the treatment of wet AMD and diabetic macular edema (DME, January 2022). The firm also launched the Elevatum trial of Vabysmo® (faricimab svoa) in patients with diabetic macular edema who come from underrepresented patient populations (April 2022).
- Harrow Health's New Drug Application (NDA) for topical AMP-100 (combination of tetracaine and chlorprocaine) for anesthesia and intraoperative pain, was accepted for review by the U.S. FDA (February 2022).
- Johnson and Johnson Vision Care received U.S. approval for its combination product, Acuvue® contact lenses eluting ketotifen for the treatment of allergic conjunctivitis (March 2022).
- Kodiak Sciences announced results of a Phase 2b/3 Study of KSI-301 in patients with wet AMD in which it was compared to aflibercept (February 2022).
- Nanoscope Therapeutics' Investigational New Drug (IND) application for a Phase 2 study of its Multi-Characteristic Opsin (MCO-010) ambient-light activatable optogenetic monotherapy to restore vision in Stargardt patients was cleared by the U.S. FDA (January 2022).
- NGM Biopharmaceuticals Inc. received Fast Track designation from the U.S. FDA for its NGM621, a monoclonal antibody inhibiting

complement C3, for the treatment of patients with geographic atrophy (GA) secondary to AMD (February 2022).

- Novartis received approval from the European Commission for its Beovu® (brolucizumab) for the treatment of visual impairment due to DME (April 2022).
- Oculis licensed from Accure Therapeutics ACT-01 (now named OCS-05), a potential small molecule therapy currently in clinical trials in patients with acute optic neuritis (March 2022).
- Ocuphire announced topline results in its MIRA-3 trial, a second Phase 3 trial of its phentolamine ophthalmic solution for the reversal of pharmacologically-induced mydriasis. The company also completed enrollment in its ZETA-1 study of oral APX3330 in patients with diabetic retinopathy and its MIRA-4 pediatric trial evaluating the safety and efficacy of phentolamine ophthalmic solution to reverse pharmacologically-induced mydriasis (March 2022).
- OKYO Pharma is developing OK-101, a lipidated chemerin peptide agonist of the ChemR23 G-protein coupled receptor, to treat dry eye disease (February 2022).
- Opthea presented data on a Phase 2B study of its intravitreal OPT-301 for the treatment of wet AMD. The data presented was in a subset of patients with polypoidal choroidal vasculopathy (February 2022).
- Outlook Therapeutics submitted a biologics license application (BLA) to the FDA for its ONS-5010 (Lytenava, bevacizumab-vikg), for the treatment of wet age-related macular degeneration (AMD) (March 2022).
- Oxurion presented new data from Part A of its two-part phase 2 clinical trial (KALAHARI) assessing THR-149, a plasma kallikrein inhibitor, for treatment of DME (February 2022).
- ProQR Therapeutics announced results from its pivotal phase 2/3 Illuminate trial of sepfarsen for the treatment of CEP290-mediated Leber's Congenital Amaurosis 10 (LCA10, February 2022).
- Ribomic announced results from its Phase 2 TOFU study of RBM-007 in patients with wet AMD (December 2022).
- Tarsus Pharmaceuticals completed enrollment of Saturn-2, its second pivotal phase 3 trial of TP-03 (lotilaner ophthalmic solution, 0.25%) for patients with Demodex blepharitis (February 2022).
- TearClear started a Phase 3 study of TC-002, its preservative-free latanoprost solution, for the treatment of glaucoma (February 2022).

Gene and cell therapy

- Regencbio presented data from its ongoing phase 2 ALTITUDE trial of RGX-314, gene therapy delivered via a NAV-AAV8 vector designed to inhibit vascular endothelial growth factor (VEGF), for the treatment of diabetic retinopathy (February 2022).
- ReNeuron announced results from a Phase 2a study of its hRPC (human retinal progenitor cells) treatment for retinitis pigmentosa (January 2022).

Other news about pharmaceutical and medical device firms

- Amylyx Pharmaceuticals presented data on its the presentation of safety and tolerability data on AMX0035 (sodium phenylbutyrate and taurursodiol) in the CENTAUR and PEGASUS clinical trials in participants with amyotrophic lateral sclerosis and Alzheimer's disease (April 2022).
- Glaukos announced the its PreserFlo™ MicroShunt PMA submission was not approved by the U.S. FDA (May 2022) [26].
- Lilly's application to the U.S. FDA for its oncology therapy, Tyvyt™ (sintilimab), based upon clinical trials conduct in China was rejected by an advisory committee. The quality of the clinical study design and conduct was cited by FDA (February 2022) [27,28].
- Pixium announced implantation in a patient with retinal degeneration of its subretinal microchip, used with glasses, to provide vision (January 2022).

- Théa purchased selected ophthalmic products from Akorn (January 2022).

Regulatory, government, and other research news

- The American Glaucoma Society issued a position statement regarding unnecessary waste associated with the use of multi-dose eyedrops and ointments in ambulatory surgery centers and operating rooms. They recommend that topical drugs in multidose containers can be used on multiple patients in surgical facilities if proper guidelines are followed (April 2022).
- *Science* magazine uncovered "journal mills" promoting fraudulent authorship in scientific journals (April 2022) [29].
- The U.S. Centers for Medicare & Medicaid Services announced they will not cover routine payment for Biogen Alzheimer's disease drug Aduhelm® (Aducanumab), but will cover the cost for patients enrolling in clinical trials (April 2022) [30].
- The impact of FDA's change in policy surrounding "unapproved" products [31] has, in the opinion of one group of researchers, been an ineffective means to encourage manufacturers to voluntarily submit safety and effectiveness data (February 2022) [32].
- The potential for clinically relevant drug-drug interactions are being discussed for Pfizer's Paxlovid (nirmatrelvir tablets and ritonavir tablets) for the treatment of mild-to-moderate COVID-19. The enzyme inhibition of ritonavir is intended to prolong the presence of nirmatrelvir. (December to March 2022). The potential for such drug-drug interaction has been previously published [33–35].
- Several pharmacies are temporarily halting filling prescriptions for stimulants from Done Health and Cerebral, Inc. with concerns for over-prescribing by clinicians at those centers. In a related item, Cerebral, Inc. is being investigated for violations of the controlled substance act (May 2022).
- The International Conference for Harmonisation published an updated E8(R1) guidance (General Considerations For Clinical Studies, (April 2022)).
- The U.S. FDA:
 - o During calendar 2021, the Center for Drug Evaluation and Research (CDER) approved 50 new drugs, either as NMEs under NDAs, or as new therapeutic biologics under Biologics License Applications (BLAs). There were five ophthalmic NDAs approved in 2021; however none was a NME, and they are not part of this list. The FDA CDER Office of Generic Drugs (OGD) approved more than 75 original Abbreviated NDAs. OGD notes that 90% of all prescriptions dispensed in the United States are for generic drugs (February 2022).
 - o Announced a proposed rule to align its Quality System Regulation (QSR, standard for manufacturing of devices) with the international standard ISO 13485:2016 (February 2022).
 - o Rejected an application by Lilly and a China-based partner to sell a new lung-cancer drug in the U.S. after agency officials raised concerns about the scientific quality of the testing in China. FDA recommended that an additional clinical trial of the drug be conducted in multiple regions (March 2022) [36]. Two subsequent applications from China-based firms for approval of oncology products based upon clinical data from China were also rejected (Hutchmed Ltd, surufatinib for the treatment of pancreatic and neuroendocrine tumors; and Shanghai Junshi Biosciences Co. and its U.S.-based partner, Coherus BioSciences, toripalimab, for the treatment of nasopharyngeal cancer) [37].
 - o Office of Clinical Pharmacology annual report noting the efforts to improve therapeutics for patients in areas such as optimizing dosing regimen, mitigating risks and assessing genetic factors (February 2022).
 - o Denied a petition by an investor to halt clinical trials of an experimental Alzheimer's drug being developed by Cassava

Sciences based upon a claim that images were manipulated (February 2022).

- o Testified to the U.S. Congress on renewal of the FDA User Fee. User fees for New Drug Applications were part of the Prescription Drug User Fee Act of 1997, and have been renewed every five years since (February 2022) [38].
- o Together with the Reagan-Udall Foundation held a public workshop to discuss naloxone access (March 2022).
- o Center for Devices and Radiological Health (CDRH) published an editorial of the regulatory issues in balancing safety and effectiveness in regulation of ophthalmic devices (April 2022) [39].
- o On the basis of a court ruling, withdrew approval of amifampridine for a pediatric subset of patients with Lambert-Eaton myasthenic syndrome. This decision and regulatory action may have an impact on the orphan designations for other product and the regulatory exclusivity granted (February 2022) [40].
- o Issued guidances for: antibody-drug combinations, immunogenicity information for therapeutic proteins, and mitigating nonhuman primate supply constraints arising from the COVID pandemic (February 2022); the impact of the Genus decision on Certain Ophthalmic Products with 21 CFR Part 4 (March 2022) [41]; Considerations for Waiver Requests for pH Adjusters in Generic Drug Products Intended for Parenteral, Ophthalmic, or Otic Use, Diversity Plans to Improve Enrollment of Participants from underrepresented Racial and Ethnic Populations in Clinical Trials Guidance for Industry, and requests for pH adjusters in generic drug products (April 2022).

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